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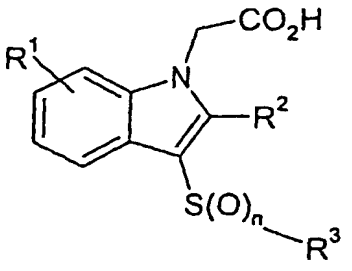
(54) Title: INDOLE-3-SULPHUR DERIVATIVES



(I)

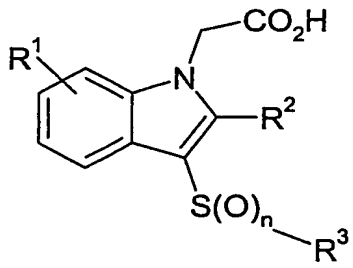
(57) Abstract: The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders. (I)

Indole-3-sulphur derivatives

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTh2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has now surprisingly been found that certain indole acetic acids are active at the CRTh2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which:

n represents 1 or 2;

R^1 is one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter five groups being optionally substituted by one or more substituents independently selected from halogen, OR^7 and NR^8R^9, NR^8R^9, $S(O)_xR^7$ where x is 0, 1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0,1 or 2;

R^3 is aryl or a 5-7 membered heteroaryl ring containing one or more heteroatoms selected from N, S and O, each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OH, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^7 and NR^8R^9, $S(O)_xR^7$ where x is 0,1 or 2;

R^4 represents aryl, heteroaryl, or C_1-C_6 alkyl, all of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} and $NR^{11}R^{12}$ $S(O)_xR^{13}$ (where x = 0, 1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;

R^5 and R^6 independently represent a hydrogen atom, a C_1-C_6 alkyl group, an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^{13} and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x is 0, 1 or 2, NR^{16}, and the ring itself optionally substituted by C_1-C_3 alkyl;

R^7 and R^{13} independently represent a C_1-C_6 alkyl group, an aryl or heteroaryl group all of which may be optionally substituted by halogen atoms;

R^8 represents a hydrogen atom, $C(O)R^9$, C_1-C_6 alkyl (optionally substituted by halogen atoms, aryl or heteraryl groups, both of which may also be optionally substituted by one or more fluorine atoms); an aryl or a heteroaryl group, which may be optionally substituted by one or more halogen atoms;

each of R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6 alkyl, an aryl or a heteroaryl group (all of which may be optionally substituted by one or more halogen atoms); and

R^{16} is hydrogen, C_{1-4} alkyl, -C(O)C_1-C_4 alkyl, C(O)YC_1-C_4alkyl, Y is O or NR^7.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear, branched or cyclic.

Aryl is phenyl and naphthyl.

When R^3 is heteroaryl, examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene.

When R^4 is heteroaryl this includes 5-7 membered aromatic rings or can be a 6,6- or 6,5-fused bicyclic ring system, each ring containing one or more heteroatoms selected from N, S and O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone.

Heterocyclic rings as defined for R^5 and R^6 means saturated heterocycles, examples include morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine.

Preferably n is 2.

Preferably R^1 is halogen, nitrile, C_{1-6}alkyl or SO_2R^4, NO_2, NR^9COR^4, $NR^9SO_2R^4$, aryl, NR^5R^6. More preferably R^1 is methyl, nitrile, chloro, SO_2Me, SO_2Et, $NHCOR^4$, $NHSO_2R^4$, phenyl, NH(alkyl).

The R^1 group(s) can be present at any suitable position on the indole ring, preferably the R^1 group(s) is (are) at the 5-position and/or 4-position. Preferably the number of substituents R^1 other than hydrogen is 1 or 2.

Preferably R^2 is C_{1-6}alkyl, more preferably methyl.

Preferably R^3 is phenyl optionally substituted by halogen, alkyl, alkoxy or nitrile. More preferably R^3 is chloro, methyl, ethyl, cyano or methoxy.

Substituents can be present on any suitable position of an R^3 group.

Preferred compounds of the invention include:

3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, sodium salt;

4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(3-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(2-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(3-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(4-cyanophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;

3-[(2-methylphenyl)sulfonyl]-2,5-Dimethyl-1*H*-indol-1-acetic acid;

3-[(2-ethylphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

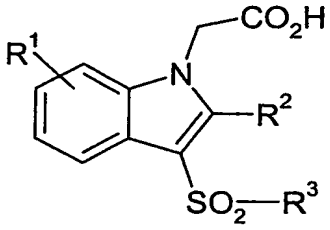
3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-nitro-1*H*-indole-1-acetic acid;

4-(acetylamino)-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-[(methylsulfonyl)amino]- 1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid;
3-[(2,6-Dichlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;
3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid
3-[(4-chlorophenyl)sulfonyl]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid,
3-[(3-chlorophenyl)sulfonyl]-5-fluoro-2-methyl- 1*H*-indole-1-acetic acid,
5-fluoro-2-methyl-3-[[4-(trifluoromethyl)phenyl]sulfonyl]- 1*H*-indole-1-acetic acid,
and pharmaceutically acceptable salts thereof.

In a further aspect the invention provides a sub-class of compounds of formula (IA):



(IA)

in which
R^1 and R^2 are independently hydrogen, halogen, CN, amino, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, SO_2C_{1-6}alkyl or $CONR^4R^5$ where R^4 and R^5 independently hydrogen or C_{1-6}alkyl; and
R^3 is phenyl substituted by halogen,
and pharmaceutically acceptable salts thereof.

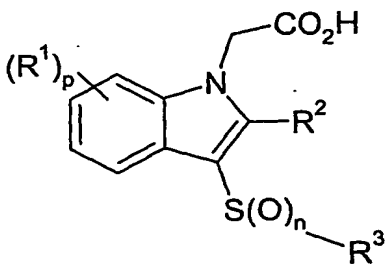
Preferably for compounds (IA) R^1 is hydrogen or C_{1-6}alkyl. More preferably R^1 is methyl. The R^1 group can be present at any suitable position on the indole ring, preferably the R^1group is at the 5-position.

Preferably for compounds (IA) R^2 is C_{1-6}alkyl, more preferably methyl.

Preferably for compounds (IA) R^3 is phenyl substituted by chloro.

Preferred compounds (IA) include:
{3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid.
and pharmaceutically acceptable salts thereof.

In a further aspect the inevtion provides a further sub-class of compounds of formula (IB):



(IB)

in which:

n represents 1 or 2;

R^1 is halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SO_2R^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2;

p is 0 to 4;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2:

R^3 is R^3 is phenyl optionally substituted by halogen;

R^4 represents hydrogen or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, $-OR^{10}$ and $-NR^{11}R^{12}$.

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, aryl, $-OR^{13}$ and $-NR^{14}R^{15}$, $-CONR^{14}R^{15}$, $-NR^{14}COR^{15}$, $-SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;

or

R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, S, NR^{16}, and itself optionally substituted by C_{1-3} alkyl, halogen;

each of R^7, R^8, R^9 R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6, alkyl, or an aryl group; and

R^{16} is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, -$COYC_1$-C_4alkyl, Y=O or NR^7.

Preferably for compounds (IB) R^1 is halogen, nitrile, C_{1-6}alkyl or SO_2R^4. More preferably R^1 is methyl, nitrile, chloro, SO_2Me, SO_2Et. Preferably p is 1 or 2.

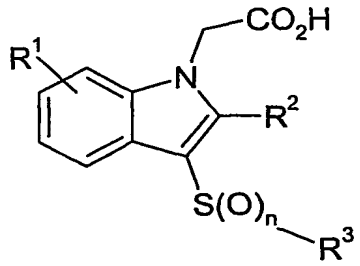
The R^1 groups can be present at any suitable position on the indole ring. preferably the R^1 group(s) is (are) at the 5-position and/or 4-position.

Preferably for compounds (IB) R^2 is C_{1-6}alkyl, more preferably methyl.

Preferably for compounds (IB) R^3 is phenyl optionally substituted by halogen, more preferably chloro.

Preferred compounds (IB) include:
{3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid,
Sodium 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetate,
and pharmaceutically acceptable salts thereof.

In a still further aspect the invention provides the use of a compound of formula (IC) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease where the inhibition of CRTh2 is beneficial:



(IC)

in which:

n represents 1 or 2;

R^1 is one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter five groups being optionally substituted by one or more substituents independently selected from halogen, OR^7 and NR^8R^9, NR^8R^9, $S(O)_xR^7$ where x is 0, 1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0,1 or 2;

R^3 is aryl or a 5-7 membered or 6,6- or 6,5-fused bicyclic aromatic ring each containing one or more heteroatoms selected from N, S and O, and each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OH, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^7 and NR^8R^9, $S(O)_xR^7$ where x is 0,1 or 2;

R^4 represents aryl, heteroaryl, or C_1-C_6 alkyl, all of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10} and $NR^{11}R^{12}$ $S(O)_xR^{13}$ (where x = 0, 1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;

R^5 and R^6 independently represent a hydrogen atom, a C_1-C_6 alkyl group, an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^{13} and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x is 0, 1 or 2, NR^{16}, and the ring itself optionally substituted by C_1-C_3 alkyl;

R^7 and R^{13} independently represent a C_1-C_6 alkyl group, an aryl or heteroaryl group all of which may be optionally substituted by halogen atoms;

R^8 represents a hydrogen atom, $C(O)R^9$, C_1-C_6 alkyl (optionally substituted by halogen atoms, aryl or heteraryl groups, both of which may also be optionally substituted by one or more fluorine atoms); an aryl or a heteroaryl group, which may be optionally substituted by one or more halogen atoms;

each of R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6 alkyl, an aryl or a heteroaryl group (all of which may be optionally substituted by one or more halogen atoms); and

R^{16} is hydrogen, C_{1-4} alkyl, -$C(O)C_1$-C_4 alkyl, $C(O)YC_1$-C_4alkyl, Y is O or NR^7.

As used below, the term "compound of formula (I)" referes to any compound above of formula (I), (IA), (IB) or (IC).

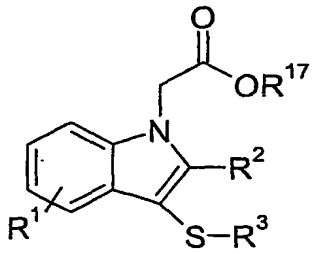
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. Preferred salts include sodium salts.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

Compounds of formula (I) can be prepared by:

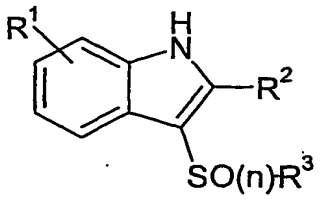
(a) oxidation of a compound of formula (II):



(II)

in which R^{17} is hydrogen or alkyl and R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, or

(b) reaction of a compound of formula (III):



(III)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (IV):

$$L\text{-}C(O)OR^{18} \quad (IV)$$

where R^{18} is an alkyl group and L is a leaving group in the presence of a base, and optionally thereafter (a) or (b) in any order:

- hydrolysing the ester group R^{17} or R^{18} to the corresponding acid
- removing any protecting group
- forming a pharmaceutically acceptable salt.

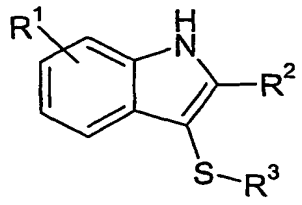
For process (a) suitable oxidising agents include MCPBA, H_2O_2 or oxone. When R^{17} is alkyl, ethyl, methyl or *tertiary*-butyl groups are prefered. Where R^{17} is hydrogen compounds of formula (I) are obtained directly by optionally removing of a protecting group and formation of appropriate salts.

Where R^{17} is alkyl the corresponding ester can be hydrolysed. Hydrolysis of the ester group R^{17} can be carried out using routine procedures, for example by stirring with base, preferably aqueous sodium or lithium hydroxide, or stirring with an acid such as TFA and optionally removing of protecting groups and formation of appropriate salts.

For process (b) the reaction can be carried out in a suitable solvent such as THF using a base such as sodium hydride or the like. Suitable groups R^{18} include C_{1-6} alkyl groups such as methyl, ethyl or *tertiary*-butyl. Suitable L is a leaving group such as halo, in particular bromo. Preferably the compound of formula (IV) is ethyl bromoacetate.

Hydrolysis of the ester group R^{18} can be carried out using routine procedures as described above for R^{17}.

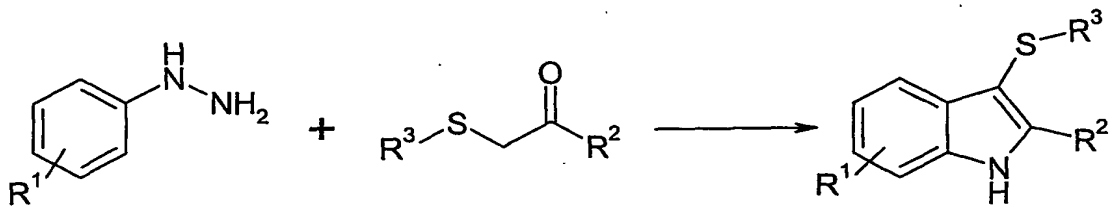
Compounds of formula (III) can be prepared by reaction of a compound of formula (V) using process (a):



(V)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with an oxidising agent, and optionally thereafter removing any protecting group.

Compounds of formula (V) where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof can be prepared by reacting a compound of formula (VI) with a compound of formula (VII):

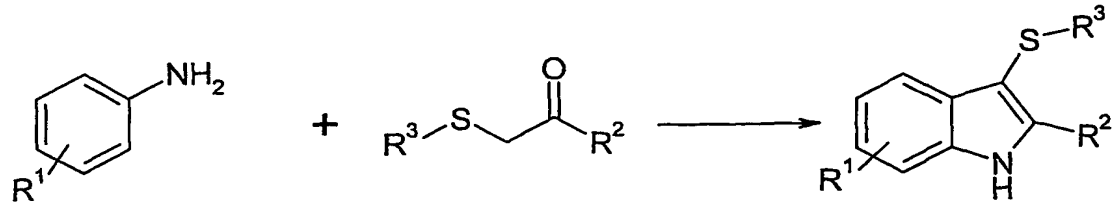


(VI) (VII) (V)

in which R^1, R^2 and R^3 are as defined in formula (I), or protected derivatives thereof.

Preferably the reaction is carried out in acetic acid with heating.

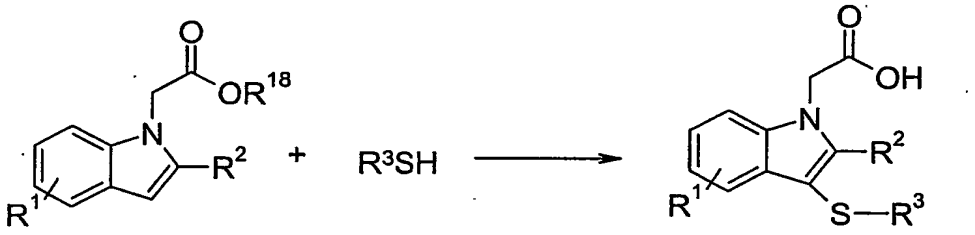
Or, compounds of formula (V) where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, can be prepared by reacting a compound of formula (VIII) with a compound of formula (VII):



(VIII) (VII) (V)

Compounds of formula (VI), ((VII) and (VIII) are commercially available or can be prepared using standard chemistry well known in the art. Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof. Preferably the reaction is carried out in a suitable solvent, such as dichloromethane or THF in the presence of a chlorinating agent such as sulfonyl cloride or *tertiary*-butyl hypochlorite.

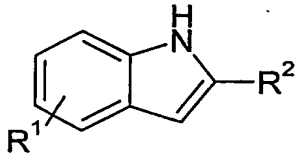
Alterantively compounds of formula (I) can be prepared by reacting compounds of formula (IX) with compounds of formula (X). Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof.



(IX) (X) (I)

Preferably the reaction is carried out in a suitable solvent such as ethanol or DMF, in the presence of iodine.

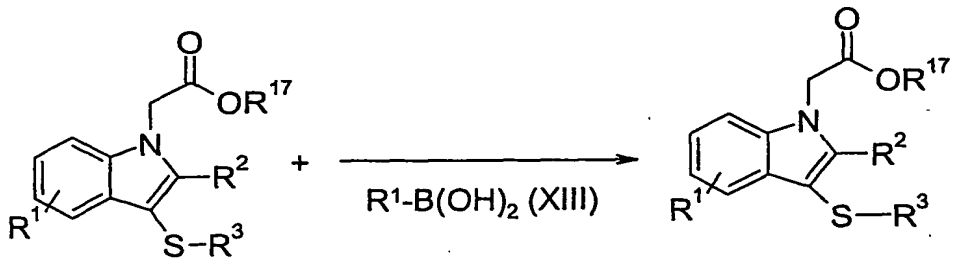
Compounds of formula (IX) can be prepared by reaction of compounds of formula (XI) and (IV) as outlined above.



(XI)

Compounds of formula (X) and (XI) are commercially available or can be prepared using standard chemistry well known in the art. Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof.

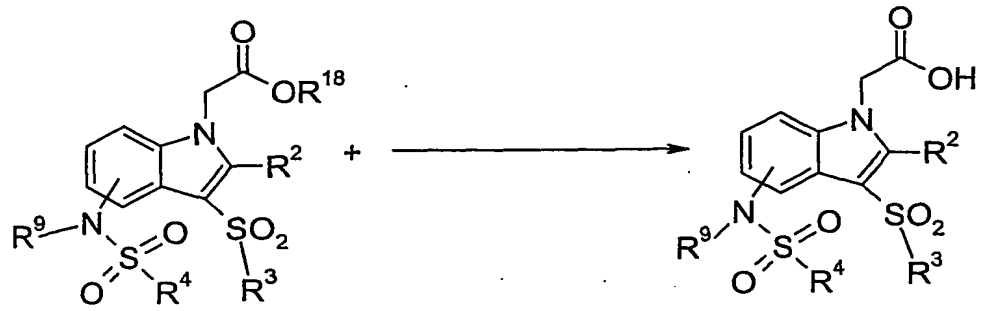
Compounds of formual (II) in which R^1 is aryl are prepared from compounds of formula (II) in which R^1 is halogen, preferably bromine or iodine using Suzuki coupling conditions, preferably using tetrakistriphenylphosphine palladium (0) as a catalyst in a suitable organic solvent, such as toluene, with heating.



(II)
R^1 = halogen

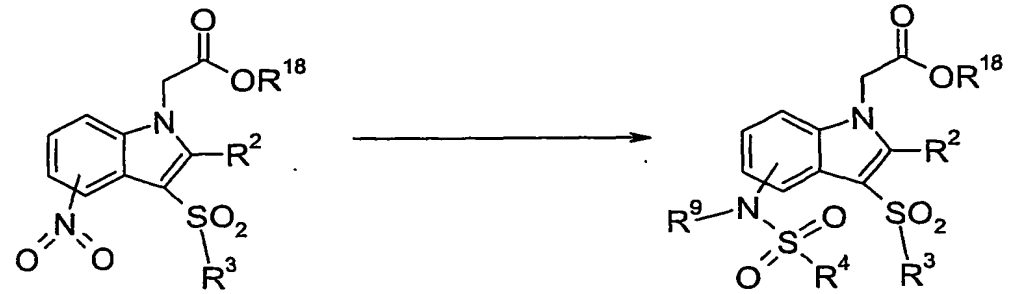
(II)
R^1 = aryl

Compounds of formula (II) in which R^1 is $NR^9SO_2R^4$ are prepared from compounds of fomula (XII) by reacting with a suitable base, preferably sodium hydroxide.



(XII) (I)

Compounds of formula (XII) are prepared from compounds of formula (XIII)



(XIII) (XII)

Compounds of formula (XIII) are hydrogenated in the presence of a suitable catalyst such as platinum on charcoal, in acidic conditions. The product of this reaction is then reacted with a sulfonyl chloride compound in the presence of a base, preferably triethylamine in an organic solvent, such as acetonitrile.

Compounds of formula (XIII) are prepared from compounds of formula (II) in which R^1 is NO_2, by reaction with a suitable oxidising agent (process A).

Compounds of formula (I) in which R^1 is NRCOR are prepared by hydrogenation of a compound of formula (II) in which R^1 is nitro, as outlined for compounds of formula (XII) above. The reduced product is then treated with an acyl chloride [$ClC(O)R^4$] in the presence of base to give a compound of formula (II), this is subsequently hydrolysed and oxidised (processes a nad b) to give a compound of formula (I) as outlined previously.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)); chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofoulous rhinitis, perennial allergic rhinitis, easonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

(2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areatacorneal ulcer and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal diorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs hepatitis (alcoholic, steatohepatitis and chronic viral) , glomerulonephritis, renal impairment, chronic renal failure and other organs

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula

(I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) the title and sub-titled compounds of the examples and methods were named using the ACD labs/name program (version 6.0) from Advanced Chemical Development Inc, Canada;

(ii) unless stated otherwise, reverse phase preparative HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(iii) Flash column chromatography refers to normal phase silica chromatography

(iv) solvents were dried with $MgSO_4$ or Na_2SO_4

(v) Evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(vi) Unless otherwise stated, operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(vii) yields are given for illustration only and are not necessarily the maximum attainable;

(viii) the structures of the end-products of the formula (1) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(ix) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), infra-red (IR) or NMR analysis;

(x) mass spectra (MS): generally only ions which indicate the parent mass are reported when given, ^1H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;

(xi) the following abbreviations are used:

EtOAc	Ethylacetate
DMF	*N,N*-Dimethyl formamide
NMP	N-methylpyrrolidine
THF	tetrahydrofuran
RT	room temperature
TFA	trifluoroacetic acid
*M*CPBA	meta-chloroperbenzoic acid

Example 1

3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

(a) 3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indole

To a solution of methylphenylhydrazine (7 g) in acetonitrile (100 ml) was added 1-[(4-chlorophenyl)thio]acetone (8.84 g) and water (10 ml). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with sodium hydrogen carbonate, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised (methanol) to give the sub-title compound (6 g).

MS: APCI+ [M+H] 288

(b) 3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole

The product of example 1 step (a) (1.85 g) was dissolved in dichloromethane (20 ml) at 0°C, to this solution MCPBA (2.85 g) was added and stirred for 2 hours. The reaction mixture was then washed with sodium carbonate solution, the organic extracts were dried with $MgSO_4$. Purification by Flash column chromatography (35% EtOAc/ hexane as eluent) gave of the sub-title compound (1.27 g).

MS: ES+ [M+H] 320

(c) 3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1- acetic acid, ethyl ester

The product of step (b) (1.27 g) was dissolved in THF (20 ml) at °C and NaH (0.115 g, 60% dispersion in oil) was added and stirred for 30 min. Ethylbromoacetate (0.66 ml) was then added and stirred for 1 h at room temperature. Ethanol was added to quench the reaction, the solvent was removed and the product washed with water and extracted with EtOAc. Purification by Flash column chromatography (30% EtOAc/hexane as eluent) gave the sub-title compound (0.716 g).

MS: ES+ [M+H] 406

(d) 3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

The product of step (c) was dissolved in ethanol (10 ml) and 10% NaOH (aq) (10 ml) was added and stirred for 1 h. The reaction mixture was then acidified with HCl (aq), and extracted with EtOAc. Purification by solid phase extraction using NH_2 sorbent (2 g),

eluting with acetonitrile followed by 10% acetic acid/acetonitrile, gave the title compound (0.301 g).

MS: ES- [M-H] 376

^{1}H NMR (DMSO) δ 2.42 (3H, s), 2.62 (3H, s), 4.68 (2H, s), 7.01 (1H, dd), 7.29 - 7.33 (1H, m), 7.58 - 7.62 (2H, m), 7.65 - 7.69 (1H, m), 7.87 - 7.93 (2H, m).

Example 2

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 5-chloro-3-[4(-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole

To a suspension of (4-chlorophenyl)-hydrazine hydrochloride (2g) in acetic acid (30ml) was added 1-[(4-chlorophenyl)thio]-acetone (2.24g), acetonitrile (20ml) and water (10ml). The mixture was strirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue suspended in EtOAc, washed with sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetic acid (20ml) and heated to 80°C overnight. The reaction mixture was poured into water, basified using NaOH and the organics extracted into EtOAc. The EtOAc was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by Flash column chromatography (20% EtOAc/hexane as eluent) gave the sub-title compound (2.2g).

^{1}H NMR ($CDCl_3$) δ 8.31 (1H,s), 7.48 (1H, d), 7.26 (2H, m), 7.13 (3H, m), 6.93 (2H, m), 2.51 (3H, s).

b) 5-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

To a solution of the product of step (a) (0.2 g) in THF (5 ml) was added 1M sodium bis(trimethylsilyl)amide solution in THF (0.65 ml). The mixture was stirred for 30 min before bromo-acetic acid, methyl ester (62 µl) was added, the reaction was stirred at room temperature overnight. A further 0.3 ml of 1.0M sodium bis(trimethylsilyl)amide solution in THF and 30 µl of methyl bromoacetate was added to the mixture and was stirred for a further 3 h. The mixture was then adsorbed onto silica and purified by Flash column chromatography (14% EtOAc/hexane as eluent) to give sub-title compound (0.21 g).

^{1}H NMR ($CDCl_3$) d 7.52 (1H, d), 7.27 (1H, d), 7.20-7.10(3H, m), 6.97-6.89 (2H, m), 4.80 (2H, d), 3.79 (3H, d), 2.47(3H, d).

c) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

To a solution of the product of step (b) (0.1 g) in dichloromethane (5 ml) was added MCPBA (121 mg). The mixture was stirred at room temperature overnight. The reaction

was diluted with dichloromethane (10 ml), washed with sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give sub-title compound (0.1 g). Used in step (d) without further purification and characterisation.

d) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

To a solution of the product from step (c) (0.09 g) in THF (5ml) was added a 1.25 M solution of NaOH(aq) (0.25 ml). The reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the residue dissolved/suspended in water. The pH was adjusted to 2 using dilute HCl (aq) and the solid which precipitated was isolated by filtration, dried under vaccum at 40 °C to give the title compound.
MS: APCI- [M-H] 398

^{1}H NMR (DMSO) δ 7.94 (2H, m), 7.89 (1H, d), 7.67-7.62 (3H, m), 7.29 (1H, m), 5.12 (2H, s), 2.63 (3H, s).

Example 3

6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 6-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (3-chlorophenyl)-hydrazine hydrochloride. Product purified using Flash column chromatography (10% EtOAc/hexane as eluent).
^{1}H NMR ($CDCl_3$) δ 8.27 (1H, s) 7.39 (1H, d) 7.34 (1H, d), 7.10 (3H, m), 6.92 (2H, m), 2.50 (3H, s).

b) 6-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (b) using the product from part (a).
^{1}H NMR ($CDCl_3$) δ 7.43 (1H, d), 7.27 - 7.25 (1H, m), 7.14-7.09 (3H, m), 6.92 (2H, dd), 4.85 (2H, s), 3.80 (3H, d), 2.46 (3H, d).

c) 6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (c) using the product from part (b). Used in step (d) without further purification or characterisation.

d) 6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) using the product from part (c).
MS: ES- [M-H] 398
^{1}H NMR (DMSO) δ 7.94-7.89 (3H, m), 7.80 (1H, d) 7.64 (2H, m), 7.27 (1H, m), 5.13 (2H,s), 2.63 (3H, s).

Example 4

7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 7-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (2-chlorophenyl)-hydrazine hydrochloride.
^{1}H NMR ($CDCl_3$) δ 8.48 (1H, s) 7.40 (1H, d), 7.19 (1H, m) 7.13-7.11 (2H, m), 7.06 (1H, t), 6.96-6.92 (2H, m), 2.55 (3H, s).

b) 7-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (b) using the product from step (a).
^{1}H NMR($CDCl_3$) δ 7.44 (1H, d), 7.18 - 7.09 (3H, m), 7.03 (1H, td), 6.92 (2H, dd), 5.37 (2H, d), 3.81 (3H, d), 2.46 (3H, d).

c) 7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (c) using the product from step (b). Used in step (d) without further purification or characterisation.

d) 7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) using the product from part (c).
MS: ES- [M-H] 398
^{1}H NMR (DMSO) δ 7.96-7.93 (3H, m), 7.65 (2H, m), 7.30 (1H, m), 7.22 (1H, t) 5.32 (2H, s), 2.70 (3H, s).

Example 5

5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indole-4-carbonitrile

A stirred solution of 1-[(4-chlorophenyl)thio]-acetone (6.14 g) in dry dichloromethane (150 ml) at –78°C was treated with sulphuryl chloride (2.25 ml). After 30 min a prepared solution of *N,N,N',N'*-tetramethyl-1,8-naphthalenediamine (6.01 g) and 5-amino-2-chloro-benzonitrile (3.89 g) in dry dicholoromethane (80 ml) was added dropwise over 30 min. The mixture was stirred for a further 2 h, after which triethylamine (4.26ml) was added and the reaction allowed to reach room temperature. The reaction mixture was diluted with dichloromethane (200ml), washed with water, 1N HCl and brine. The organic phase was dried ($MgSO_4$), evaporated *in vacuo*, and the residue purified by flash column chromatography eluting with iso-hexane and ethyl acetate (1:1) to give the sub-title compound (1 g), and the regioisomer (600 mg) used in example 6 below.

^{1}H NMR $CDCl_3$: δ 12.52 (s,1H), 7.74 (d, 1H), 7.38 (dd, 1H), 7.29 (m, 2H), 6.97 (m, 2H), 3.29 (s, 3H).

b) 3-[(4-chlorophenyl)thio]-4-cyano-2,5-dimethyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 1 part (c) using the product of part (a).

^{1}H NMR $CDCl_3$: δ 7.37 (1H, d), 7.30 (1H, d), 7.18 - 7.13 (2H, m), 7.00-6.96 (2H, m), 4.92 (2H, m), 3.80 (3H, m), 2.55 (3H, s).

(c) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepard by the method if example 1 part (b) from the product of part (b).

(d) 5-Chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 1 part (d) using the product of part (c).

^{1}H NMR DMSO : δ 2.81(3H, s), 5.29 (2H, s), 7.62 (1H, s), 7.7 (2H, m), 7.98(2H, m) and 8.08(1H, d).

MS: APCI+ [M+H] 422

Example 6

5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-6-carbonitrile

Obtained from example 5 part (a)

^{1}H NMR $CDCl_3$: δ 8.68 (1H, s), 7.69 (1H, s), 7.61 (1H, s), 7.15 (2H, dt), 6.91 (2H. dt), 2.57 (3H, s).

b) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid

Prepared by the method of example 2 part (d) to give the title compound as a white solid.

^{1}H NMR DMSO: δ 8.42 (1H, s), 7.59 (1H, s), 7.3 (2H, dt), 6.99 (2H, dt), 5.24 (2H, s), 2.46 (3H, s).

M.pt 256-258°C

MS: APCI [M-H] 389

Example 7

3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid, ethyl ester

MCPBA (1.07 g) was added to a solution of example 1 part a) (1.79 g) in dichloromethane (20 ml) at 0°C. The reaction mixture was stirred for 1h, after which further mCPBA (53 mg) was added and stirred for a further 30 min. The reaction mixture was allowed to reach room temperature and the sub-title compound was obtained as a white solid after filtration (0.68 g). Used directly in the next step without further purification.

b) 3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

NaH (0.13 g, 60% dispersion in mineral oil) was added to the product from part (a) (0.685 g) in THF at 0°C. The reaction mixture was stirred for 30 min and then ethyl bromoacetate (0.26 ml) was added and the mixture stirred for 1h. Ethanol was added and then concentrated *in vacuo*. The product was extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid (761 mg). The solid was dissolved in ethanol (15 ml), NaOH (10% solution, 5 ml) and then the solution stirred overnight. The reaction mixture was acidified (dilute HCl) and extracted with EtOAC. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified with amine resin, eluting with MeCN and then 5% acetic acid in MeCN to give the title compound (60 mg).

^{1}H NMR DMSO: δ 7.61 (4H, s), 7.2-7.25 (1H, m), 6.88-6.91 (1H, m), 6.88-6.86 (1H, m), 4.43 (2H, s), 2.57 (3H, s) and 2.21 (3H, s).

Example 8

3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole

Prepared by the method of example 5 part (a) from 5-(ethylsulfonyl)-2-methoxy-benzenamine.

^{1}H NMR $CDCl_3$: δ 9.00 (1H, s), 7.91 (1H, d), 7.12 (2H, dd), 6.86 (2H, m), 6.73 (1H,d), 4.05 (3H, s), 3.46 (2H,q), 2.46 (3H, s) and 1.16 (3H, t).

b) 3-[(4-chlorophenyl)thio]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid, methyl ester

Prepared by the method of example 5 part (b), using the product of sterp (a.)

^{1}H NMR $CDCl_3$: δ 7.92 (1H, d), 7.13 (2H, dt), 6.85 (2H, dt), 6.73 (1H,d), 5.27 (2H,s), 3.98 (3H, s), 3.79 (3H, s), 3.48 (2H, q), 2.38 (3H,s) and 1.18 (3H, t).

c) 3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid, methyl ester

Prepared by the method of example 5 part (c) using the product of step (b).

MS: ES+ [M+H] 435

d) 3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid

Prepared by the method of example 5 part (d) using the product of step (c).

^{1}H NMR DMSO: δ 7.79 (1H, d), 7.73 (2H, d), 7.58 (2H, d), 7.04 (1H, d), 5.07 (2H, s), 3.95 (3H, s), 3.58 (2H, q), 2.66 (3H,s) and 1.23 (3H, t).

Example 9

3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-5-cyano-2-methyl-1*H*-indole

To a stirred solution of 4-aminobenzonitrile (5 g) in dichloromethane (150 ml) cooled to ⁻70°C was added t-butyl hypochlorite (4.6 g) dropwise over 5 mins. The reaction was

stirred for 10 mins before 1-[4-chlorophenyl)thio]-2-propanone (8.49g) was added as a solution in dichloromethane (20 ml). After 1 h triethylamine (5.9 ml) was added and the reaction allowed to warm to room temperature. The reaction was diluted with dichloromethane, washed with HCl (aq), brine, dried over $MgSO_4$, and concentrated in vacuo to give a brown solid. Purification by recystallisation from Methanol gave the subtitle compound (7.5 g).

^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.84 (s, 1H), 7.44 (dd, 1H), 7.41 (d, 1H), 7.19-7.08 (m, 2H), 6.93 (dd, 2H), 2.56 (s, 3H).

b) 3-[(4-chlorophenyl)thio]-5-cyano-2-methyl-1*H*-indole-acetic acid, ethyl ester

The subtitle compound was prepared by the method of example 5 part (b) using the product from part (a) and ethyl bromoacetate. The product was used without further characterisation in part (c).

c) 3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester

mCPBA (128 mg) was added to the product of part (b) (200 mg) in dichloromethane (10 ml), and stirred overnight. The solution was washed ($NaHCO_3$), brine, then dried ($MgSO_4$) and concentrated *in vacuo* to give the subtitle compound as a white solid (170 mg).

d) 3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 5 part (d) using the product of step (c).

^{1}H NMR (DMSO) δ 7.69-7.57 (m, 6H), 7.51 (dd, 1H), 4.85 (dd, 2H) and 2.63 (s, 3H)

Example 10

3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 1*H*-indole-1-acetic acid, 3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 5 part (c) using the product of example 9 part (b).

^{1}H NMR (DMSO) δ 8.35 (d, 1H), 8.03 (dt, 2H), 7.82 (d, 1H), 7.71-7.62 (m, 3H), 5.32 (s, 2H), 4.15 (q, 2H), 2.67 (s, 3H) and 1.18 (td, 3H)

b) 1*H*-indole-1-acetic acid, 3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepeared by the method of example 5 part (d) using the product of step (a)

^{1}H NMR (DMSO) δ 8.35 (d, 1H), 8.05-8.01 (m, 2H), 7.82 (d, 1H), 7.69-7.63 (m, 3H), 5.20 (s, 2H) and 2.67 (s, 3H).

Example 11

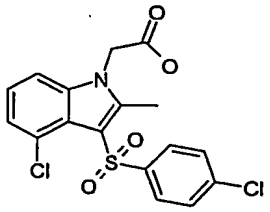
Sodium 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetate

Sodium hydroxide (1M, 4.3 ml) was added to a solution of the product of example 1 part (c) (1.75 g) in THF (60 ml). The reaction mixture was stirred overnight and then concentrated *in vacuo*. The residue was recrystallised from water to give the title compound as a white solid.

^{1}H NMR (DMSO) δ 7.89 (dd, 2H), 7.66 (d, 1H), 7.61 (m, 2H), 7.26(d, 1H.), 6.99 (1H, dd), 4.39(s, 2H), 2.59 (s, 3H) and 2.4(s, 3H).

Example 12

4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid



a) 4-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (3-chlorophenyl)-hydrazine hydrochloride. Product purified using Flash column chromatography (10%EtOAc/hexane as eluent).

^{1}H NMR ($CDCl_3$) δ 8.38 (1H, s), 7.27 - 7.24 (2H, m), 7.15 - 7.11 (2H, m), 7.09 - 7.08 (1H, m), 6.96 (2H, dt), 2.52 (3H, s)

b) 4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 1 part (b) using the product from part (a). Product was purified using Flash column chromatography (33%EtOAc/hexane as eluent).

^{1}H NMR (DMSO) δ 12.57 (1H, s), 7.83 (2H, dt), 7.60 (2H, dt), 7.41 (1H, dd), 7.18 - 7.08 (2H, m), 2.80 (3H, s)

c) 4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

The subtitle compound was prepared by the method of example 1 part (c) using the product from part (b). Product was purified using Flash column chromatography (33%EtOAc/hexane as eluent).

^{1}H NMR (DMSO) δ 7.80 (2H, dt), 7.63 (3H, m), 7.25 – 7.16 (2H, m), 5.36 (2H, s), 4.20, (2H, q), 2.81 (3H, s), 1.23 (3H, t).

d) 4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

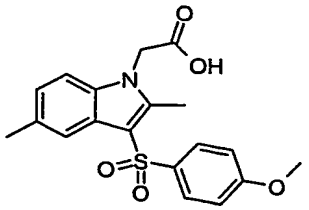
The title compound was prepared by the method of example 2 part (d) using the product from part (c). Product was purifed using reverse phase preparative HPLC (eluent $MeCN/NH_3(aq)$).

^{1}H NMR (DMSO) δ 7.79 (2H, dt), 7.62 (2H, dt), 7.52 (1H, dd), 7.19 – 7.11 (2H, m), 4.84 (2H, s), 2.78 (3H, s).

APCI- (M-H) 395.

Example 13

3-[(4-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid



a) 2,5-dimethyl-1*H*-indol-1-acetic acid

60% sodium hydride/oil (0.64 g) was added to a solution of 2,5-dimethyl-1*H*-indole (2.0g) in DMF (15ml). After 15 min ethyl bromoacetate (2.7 ml) was added quickly and the reaction stirred for 20 min. The mixture was quenched with 1% aqueous acetic acid (100 ml), extracted with ethyl acetate (2 x 100ml) and washed with water (2 x 50 ml) and brine (20 ml). The extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a brown solid. The solid was dissolved in EtOH (20ml) and aqueous sodium hydroxide (1M,10ml) added. After 1 h the solution was adjusted to pH6 with aqueous hydrochloric acid (1M,~10ml), and then evaporated *in vacuo*. The residue was purified by flash column chromatography (gradient 1-10% methanol in dichloromethane). The sub-title compound was obtained as a red/brown solid (1.3 g).

MS: APCI+ [M+H] 204

^{1}H NMR $\delta_{(DMSO)}$ 7.22 - 7.17 (2H, m), 6.85 (1H, d), 6.11 (1H, s), 4.87 (2H, s), 2.34 (3H, s), 2.30 (3H, s)

b) 3-[(4-methoxyphenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, ammonium salt

Iodine (0.51 g) was added to a solution of 4-methoxylbenzenethiol (0.25 g) and the product from example 13 step a) (0.2 g) in DMF (5 ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.27 g).

MS (APCI-) 340 $[(M-NH_4)-H]^-$

^{1}H NMR $\delta_{(DMSO)}$ 7.24 (1H, d), 7.15 (1H, s), 6.95 (2H, d), 6.90 (1H, d), 6.78 (2H, d), 4.60 (2H, s), 3.66 (3H, s), 2.38 (3H, s), 2.33 (3H, s)

c) 3-[(4-methoxyphenyl)sulfonyl]- 2,5-Dimethyl-1*H*-indol-1-acetic acid

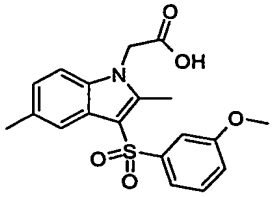
3-Chlorobenzenecarboperoxoic acid (0.44 g) was added to a solution of the product from example 13 step ii) (0.2 g) in acetonitrile (4 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15 min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (98 mg).

MS: APCI- [M-H] 372

^{1}H NMR $\delta_{(DMSO)}$ 7.83 (2H, d), 7.69 (1H, s), 7.33 (1H, d), 7.09 - 6.98 (1H, m), 7.06 (2H, d), 4.79 (3H, s), 3.78 (3H, s), 2.59 (3H, s), 2.40 (3H, s)

Example 14

3-[(3-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid



a) 3-[(3-methoxyphenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid

Iodine (0.51 g) was added to a solution of 3-methoxylbenzenethiol (0.25 g) and the product from example 13 step i) (0.2 g) in DMF (5ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.22 g).

MS: APCI- [M-H] 340

^{1}H NMR $\delta_{(DMSO)}$ 7.40 (1H, d), 7.16 (1H, s), 7.11 (1H, t), 6.98 (1H, d), 6.63 (1H, d), 6.55 (1H, d), 6.45 (1H, s), 5.08 (2H, s), 3.61 (3H, s), 2.39 (3H, s), 2.34 (3H, s)

b) 3-[(3-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

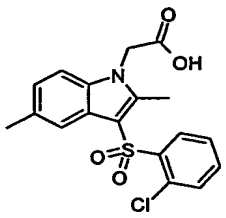
3-Chlorobenzenecarboperoxoic acid (0.4 g) was added to a solution of the product from example 14 step i) (0.18 g) in acetonitrile (4 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (70 mg).

MS: APCI- [M-H] 372

^{1}H NMR $\delta_{(DMSO)}$ 7.69 (1H, s), 7.48 - 7.43 (2H, m), 7.36 - 7.32 (1H, m), 7.31 (1H, d), 7.18 - 7.11 (1H, m), 7.01 (1H, d), 4.66 (2H, s), 3.78 (3H, s), 2.61 (3H, s), 2.40 (3H, s)

Example 15

3-[(2-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid



a) 3-[(2-Chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, sodium salt

Iodine (0.22 g) was added to a solution of 2-chlorobenzenethiol (0.13 g) and the product from example 13 step a) (015 g) in EtOH (5ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* to yield the product as a colourless oil. The oil was then dissolved in MeOH (10 ml) treated with aqueous sodium hydroxide (1M,0.52 ml) and evaporated *in vacuo* to yield the sodium salt as a white solid (0.13 g).

MS: APCI- [M-Na] 344

^{1}H NMR $\delta_{(DMSO)}$ 7.28 - 7.15 (2H, m), 7.13 - 7.06 (2H, m), 6.97 - 6.88 (3H, m), 4.42 (2H, s), 2.36 (3H, s), 2.33 (3H, s)

b) 3-[(2-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

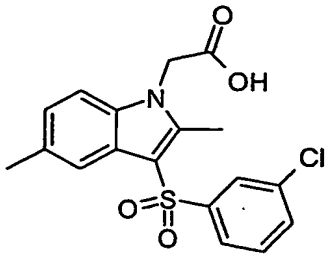
3-Chlorobenzenecarboperoxoic acid (0.14 g) was added to a solution of the product from example 15 step a) (0.07 g) in acetonitrile (2 ml) and water (0.5 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2ml) added and stirred for a further 15 min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (11 mg).

MS APCI- $[M-H]^-$ 376

^{1}H NMR $\delta_{(DMSO)}$ 8.32 - 8.25 (1H, m), 7.64 - 7.52 (3H, m), 7.39 (1H, s), 7.34 (1H, d), 6.99 (1H, d), 4.73 (2H, s), 2.59 (3H, s), 2.32 (3H, s)

Example 16

3-[(3-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid



a) 3-[(3-Chlorophenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, sodium salt

Iodine (0.29 g) was added to a solution of 3-chlorobenzenethiol (0.175 g) and the product from example 13 step a) (0.2 g) in EtOH (5 ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* to yield the product as a colourless oil. The oil was then dissolved in MeOH (10ml) treated with aqueous sodium hydroxide (1M,0.52 ml) and evaporated *in vacuo* to yield the sodium salt as a white solid (0.19 g).

MS (APCI-) 344 $[(M-Na)-H]^-$

^1H NMR $\delta_{(DMSO)}$ 7.28 - 7.15 (2H, m), 7.13 - 7.06 (2H, m), 6.97 - 6.88 (3H, m), 4.42 (2H, s), 2.36 (3H, s), 2.33 (3H, s)

b) 3-[(3-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

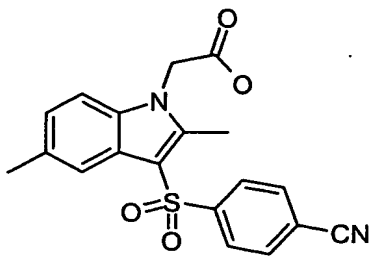
3-Chlorobenzenecarboperoxoic acid (0.32 g) was added to a solution of the product from example 16 step a) (0.16 g) in acetonitrile (4 ml) and water (1 ml). The reaction was stirred for 1 h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (65 mg).

MS APCI-$[M-H]^-$376

^1H NMR $\delta_{(DMSO)}$ 7.87 (2H, d), 7.68 (2H, d), 7.63 - 7.56 (1H, m), 7.36 (1H, d), 7.04 (1H, d), 4.79 (2H, s), 2.62 (3H, s), 2.41 (3H, s)

Example 17

3-[(4-Cyanophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid



a) 3-[(4-Cyanophenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, ammonium salt

Iodine (0.51 g) was added to a solution of 4-cyanobenzenethiol (0.27 g) and the product from example 13 step a) (0.2 g) in DMF (5 ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.25 g).

MS APCI- $[(M-NH_4)-H]^-$ 334

^1H NMR $\delta_{(DMSO)}$ 7.62 (2H, d), 7.35 (1H, d), 7.10 (1H, s), 7.08 (2H, d), 6.97 (1H, d), 4.80 (2H, s), 2.36 (3H, s), 2.32 (3H, s)

b) 3-[(4-Cyanophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

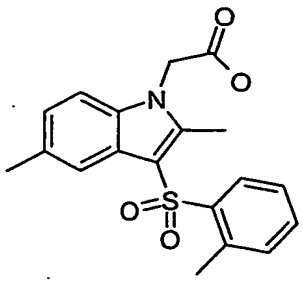
3-Chlorobenzenecarboperoxoic acid (0.44 g) was added to a solution of the product from example 17 step a) (0.21 g) in acetonitrile (4 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (58 mg).

MS (APCI-) $[M-H]^-$ 367

^1H NMR $\delta_{(DMSO)}$ 8.04 (4H, dd), 7.69 (1H, s), 7.36 (1H, d), 7.04 (1H, d), 4.76 (2H, s), 2.61 (3H, s), 2.41 (3H, s)

Example 18

3-[(2-methylphenyl)sulfonyl]-2,5-Dimethyl-1*H*-indol-1-acetic acid



a) 3-[(2-methylphenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, ammonium salt

Iodine (0.29 g) was added to a solution of 2-methylbenzenethiol (0.16 g) and the product from example 13 step a) (0.2 g) in DMF (5 ml). After 1 h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.19 g).

MS APCI- $[(M-NH_4)-H]^-$ 324

^1H NMR $\delta_{(DMSO)}$ 7.24 (1H, d), 7.15 (1H, d), 7.07 (1H, s), 6.97 - 6.86 (3H, m), 6.47 (1H, d), 4.49 (2H, s), 2.42 (3H, s), 2.33 (3H, s), 2.31 (3H, s)

b) 3-[(2-methylphenyl)sulfonyl]-2,5-Dimethyl-1*H*-indol-1- acetic acid

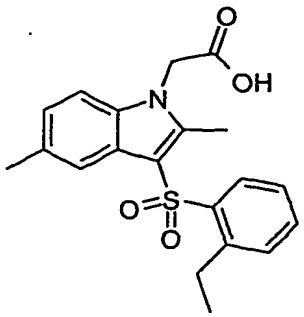
3-Chlorobenzenecarboperoxoic acid (0.32 g) was added to a solution of the product from example 18 step a) (0.14 g) in acetonitrile (4 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (65 mg).

MS APCI- $[M-H]^-$ 356

^1H NMR $\delta_{(DMSO)}$ 8.05 (1H, d), 7.54 - 7.40 (2H, m), 7.44 (1H, s), 7.40 (1H, d), 7.31 (1H, d), 7.01 (1H, d), 4.94 (2H, s), 2.54 (3H, s), 2.38 (3H, s), 2.33 (3H, s)

Example 19

3-[(2-ethylphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid



a) 3-[(2-ethylphenyl)thio]-2,5-dimethyl-1*H*-indol-1-acetic acid, ammonium salt

Iodine (0.44 g) was added to a solution of 2-ethylbenzenethiol (0.32 g) and the product from example 13 step a) (0.2 g) in DMF (5 ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.18 g).

MS (APCI-) 338 $[(M-NH_4)-H]^-$

^{1}H NMR $\delta_{(DMSO)}$ 7.26 (1H, d), 7.16 (1H, d), 7.08 (1H, s), 7.01 - 6.85 (3H, m), 6.48 (1H, d), 4.57 (2H, s), 2.83 (2H, q), 2.34 (3H, s), 2.31 (3H, s), 1.31 (3H, t)

b) 3-[(2-ethylphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid

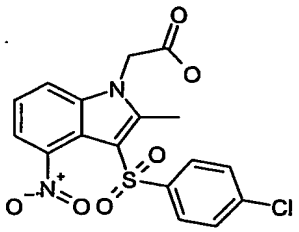
3-Chlorobenzenecarboperoxoic acid (0.32 g) was added to a solution of the product from example 19 step a) (0.14 g) in acetonitrile (4 ml). The reaction was stirred for 1h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15 min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (45 mg).

MS APCI- $[M-H]^-$ 370

^{1}H NMR $\delta_{(DMSO)}$ 7.95 (1H, d), 7.58 - 7.50 (1H, m), 7.47 (1H, s), 7.44 - 7.34 (3H, m), 7.00 (1H, d), 4.81 (2H, s), 2.87 (2H, q), 2.51 (3H, s), 2.33 (3H, s), 0.94 (3H, t)

Example 20

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-nitro-1*H*-indole-1-acetic acid



a) 3-[(4-chlorophenyl)thio]-2-methyl-4nitro-1*H*-indole

To a stirred solution of 3-nitroaniline (8 g) in THF (700 ml) cooled to –78°C was added t-butyl hypochlorite (6.3 g) dropwise over 5 minutes. The reaction was allowed to warm to –65°C over 20 minutes before 1-[4-chlorophenyl)thio]-2-propanone (11.6 g) was added as a solution in tetrahydrofuran (20 ml). After 2 hours triethylamine (8.1 ml) was added and the reaction allowed to warm to room temperature. 2M HCl(aq) was added to the reaction mixture before concentration *in vacuo*. The residue was slurried in methanol and the solid which precipitated isolated by filtration to give the subtitle compound (5.8 g).

^{1}H NMR (DMSO) δ12.55 (s, 1H), 7.76 (dd, 1H), 7.63 (dd, 1H), 7.31-7.22 (m, 3H), 6.91 (dd, 2H), 2.47 (s, 3H)

b) 3-[(4-chlorophenyl)thio]-2-methyl-4nitro-1*H*-indole-acetic acid, ethyl ester

To a stirred suspension of sodium hydride, 60% dispersion in mineral oil, (0.85 g) in THF (100 ml) was added the product from part (a) (5.6 g) as a solution in THF (50 ml). After stirring at room temperature for 30 minutes ethyl bromoacetate (2.3 ml) was added dropwise over 10 minutes. After 2 hours the reaction was concentrated *in vacuo*, the residue dissolved in ethyl acetate, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from boiling ethanol gave the subtitle compound (5 g).

^{1}H NMR (DMSO) δ7.97 (dd, 1H), 7.65 (dd, 1H), 7.35 (t, 1H), 7.26 (dt, 2H), 6.92 (dt, 2H), 5.40 (s, 2H), 4.19 (q, 2H), 2.45 (s, 3H), 1.22 (t, 3H).

c) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4nitro-1*H*-indole-acetic acid, ethyl ester

To a solution of the product from part (b) (0.2 g) in dichloromethane (10 ml) was added MCPBA (0.245 g). After strring overnight a further 20ml of dichloromethane was added to the reaction before the mixture was washed with sodium hydrogen carbonate solution,

brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was used without further characterisation in step (d).

d) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4nitro-1*H*-indole-acetic acid

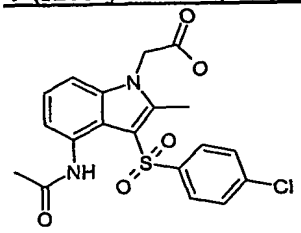
The title compound was prepared by the method of example 2 part (d) using the product from part (c). Product was purified using reverse phase preparative HPLC (eluent MeCN/NH_3 (aq)).

^{1}H NMR (DMSO) δ 7.97 (1H, dd), 7.85 (2H, dt), 7.68 (2H, m), 7.65 (1H, d), 7.40 (1H, t), 5.10 (2H, s), 2.77 (3H, s).

APCI- (M-H) 407

Example 21

4-(Acetylamino)-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid



a) 4-amino-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

A suspension of the product from example 20 part (b) (2.25 g) in ethanol (170 ml) was stirred in the presence of 5%Pt/C (0.5 g) under 2 bar pressure of H_2. After stirring overnight the catalyst was removed by filtration and the filtrates concentrated *in vacuo*. Purification by flash column chromatography (14% EtOAc/hexane as eluent) gave the subtitle compound (1.4 g).

^{1}H NMR (DMSO) δ 7.30 (dd, 2H), 7.0 (dt, 2H), 6.85 (t, 1H), 6.68 (dd, 1H), 6.23 (dd, 1H), 5.33 (s, 2H), 5.09 (s, 2H), 4.16 (q, 2H), 2.33 (s, 3H), 1.21 (t, 3H).

3-[(4-chlorophenyl)thio]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid, ethyl ester was also isolated as a by product from the reaction (0.33g).

^{1}H NMR (DMSO) δ 7.32 (dd, 2H), 7.01 (dd, 2H), 6.95 (t, 1H), 6.73 (d, 1H), 6.16 (d, 1H), 5.70 (t, 1H), 5.11 (s, 2H), 4.16 (q, 2H), 3.05 (dt, 2H), 2.34 (s, 3H), 1.21 (t, 3H), 1.02 (t, 3H).

b) 4-(acetylamino)-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-acetic acid, ethyl ester

To a solution of the product from part (a) (0.5 g) in dichloromethane (10 ml) was added triethylamine (0.18 ml) and acetyl chloride (0.1 ml), the reaction was stirred at room temperature for 30 minutes. The mixture was then adsorbed onto silica gel and purified by flash column chromatography (33% EtOAc/hexane as eluent) to give the subtitle compound (0.52 g).

^{1}H NMR (DMSO) δ 9.51 (s, 1H), 7.46 (d, 1H), 7.34 – 7.27 (m, 3H), 7.11(t, 1H), 6.97 (d, 2H), 5.24 (s, 2H), 4.18 (q, 2H), 2.39 (s, 3H), 1.86 (s, 3H), 1.21 (t, 3H).

c) 4-(acetylamino)-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

The subtitle compound was prepared by the method of example 20 part (c) using the product from part (b). Used without further characterisation in part (d).

d) 4-(acetylamino)-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

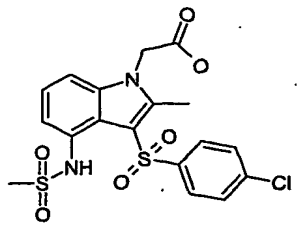
The title compound was prepared by the method of example 2 part (d) using the product from part (c). Product was purified using reverse phase preparative HPLC (eluent MeCN/NH_3(aq)).

^{1}H NMR (DMSO) δ 10.34 (1H, s), 8.01 (1H, d), 7.77 (2H, dt), 7.67 (2H, m), 7.29 (1H, d), 7.19 (1H, t), 4.82 (2H, s), 2.66 (3H, s), 2.06 (3H, s).

APCI- (M-H) 419

Example 22

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-[(methylsulfonyl)amino]- 1*H*-indole-1-acetic acid



a) 4-amino-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, ethyl ester

A suspension of the product from example 20 part (c) (1 g) in glacial acetic acid (50 ml) was stirred in the presence of 5% Pt/C (0.5 g) under 3 bar pressure of H_2 for 24 hours. The catalyst was removed by filtration and the filtrates concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/hexane as eluent) gave the subtitle compound (0.45 g).

^{1}H NMR (DMSO) δ 7.89 (2H, dt), 7.66 (2H, dt), 6.96 (1H, t), 6.72 (1H, d), 6.45 (1H, d), 5.96 (2H, s), 5.13 (2H, s), 4.14 (2H, q), 2.63 (3H, s), 1.18 (3H, t)

3-[(4-chlorophenyl)sulfonyl]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid, ethyl ester was isolated as a by product from the reaction.

^{1}H NMR (DMSO) δ 7.83 (2H, dd), 7.67 (2H, dt), 7.06 (1H, t), 6.78 (1H, d), 6.72 (1H, t), 6.31 (1H, d), 5.16 (2H, s), 4.15 (2H, q), 3.12 (2H, dt), 2.65 (3H, s), 1.28 - 1.16 (6H, m)

b) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-[(methylsulfonyl)amino]-1*H*-indole-1-acetic acid, ethyl ester

To a solution of the product from part (a) (0.2 g) in acetonitrile (10 ml) was added triethylamine (72 ul) and methane sulfonylchloride (41ul), the reaction was heated to reflux overnight. The mixture was then adsorbed onto silica gel and purified by flash column chromatography (33% EtOAc/hexane as eluent) to give the subtitle compound (0.18 g)

^{1}H NMR (DMSO) δ 9.83 (1H, s), 7.84 (2H, d), 7.71 (2H, d), 7.40 (1H, d), 7.33 - 7.27 (2H, m), 5.31 (2H, s), 4.17 (2H, q), 2.99 (3H, s), 2.68 (3H, s), 1.20 (3H, t)

c) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-[(methylsulfonyl)amino]- 1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) using the product of part (b). The product was recystallised from boiling aqueous ethanol.

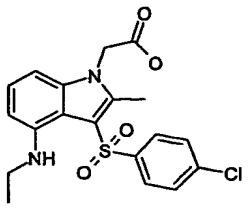
^{1}H NMR (DMSO) δ 9.84 (1H, s), 7.84 (2H, dt), 7.71 (2H, dt), 7.40 (1H, dd), 7.33 - 7.27 (2H, m), 5.15 (2H, s), 2.98 (3H, s), 2.68 (3H, s)

MS: APCI- [M-H] 455

m.p. dec>237°C

Example 23

3-[(4-chlorophenyl)sulfonyl]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid



a) 3-[(4-chlorophenyl)sulfonyl]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid

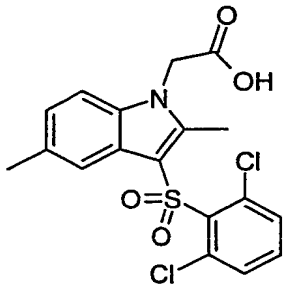
The title compound was prepared by the method of example 2 part (d) using the by product from example 22 part (a). Product was purified using reverse phase preparative HPLC.

^{1}H NMR (DMSO) δ 7.83 (2H, dt), 7.65 (2H, dt), 7.02 (1H, t), 6.73 - 6.69 (2H, m), 6.27 (1H, d), 4.68 (2H, s), 3.12 (2H, dt), 2.62 (3H, s), 1.25 (3H, t)

MS: APCI- [M-H] 405

Example 24

3-[(2,6-Dichlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid



a) 3-[(2,6-Dichlorophenyl)thio]-2,5-dimethyl-1*H*-indole-1-acetic acid

Iodine (0.51 g) was added to a solution of 2,6-dichlorobenzenethiol (0.36 g) and the product from example 13 step a) (0.2 g) in DMF (5 ml). After 1h the solution was purified by reverse phase HPLC. The solvent was evaporated *in vacuo* and the oily residue treated with ether to give a solid. Filtered off and dried to yield the title compound as a white solid (0.22 g).

MS: APCI- $[M-H]^-$ 378

^{1}H NMR $\delta_{(DMSO)}$ 7.49 (2H, d), 7.29 (1H, m), 7.24 (1H, d), 7.13 (1H, s), 6.88 (1H, d), 4.81 (2H, s), 2.44 (3H, s), 2.29 (3H, s)

b) 3-[(2,6-Dichlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

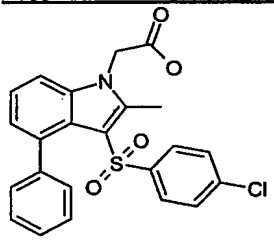
3-Chlorobenzenecarboperoxoic acid (0.34 g) was added to a solution of the product from example 24 step a) (0.18 g) in acetonitrile (5 ml) and water (0.5 ml). The reaction was stirred for 1 h, 1M aqueous sodium thiosulphate (2 ml) added and stirred for a further 15 min. The mixture was filtered, purified by reverse phase HPLC and evaporated *in vacuo* to yield the title compound as a white solid (40 mg).

MS: APCI- 410 $[M-H]^-$

^{1}H NMR $\delta_{(DMSO)}$ 7.64 - 7.60 (2H, m), 7.57 - 7.51 (1H, m), 7.45 (1H, s), 7.42 (1H, d), 7.03 (1H, d), 5.01 (2H, s), 2.60 (3H, s), 2.33 (3H, s)

Example 25

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid



a) 4-bromo-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (3-bromophenyl)-hydrazine hydrochloride. Product purified using Flash column chromatography (10%EtOAc/hexane as eluent).

^{1}H NMR($CDCl_3$) δ 7.31 (1H, s), 7.30 (2H, d), 7.13 (2H, dt), 7.02 (1H, t), 6.94 (2H, dt), 2.52 (3H, s).

b) 4-bromo-3-[(4-chlorophenyl)thio]-2-methyl-1H-indole-1-acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 20 part (b) using the product of part (a) and t-butylbromoacetate. Product was purified using Flash column chromatography

(10%EtOAc/hexane as eluent).

^{1}H NMR($CDCl_3$) d 7.31 (1H, dd), 7.21 (1H, dd), 7.14 – 7.10 (2H, m), 7.05 (1H, t), 6.94 – 6.91 (2H, m), 4.77 (2H, s), 2.49 (3H, s), 1.43 (9H, s).

c) 3-[(4-chlorophenyl)thio]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester

To a solution of the product of part (b) (0.5 g) in ethanol (0.8 ml) and toluene (3 ml) was added 2 M sodium carbonate solution in water (1.4 ml), phenylboronic acid (0.131 g) and tetrakis(triphenylphosphine)palladium(0) (1.2 g). The reaction was heated to reflux for 2 hours, cooled and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the subtitle compound (0.4 g).
^{1}H NMR (DMSO) d 7.53 (1H, d), 7.25–7.18 (2H, m), 7.15 – 7.09 (6H, m), 6.87 (1H, d), 6.54 (2H, m), 5.17 (2H, s), 2.39 (3H, s), 1.43 (9H, s).

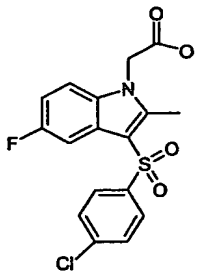
d) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method fo example 20 part (c) using the product from part (c). The product was used without further characterisation in part (e).

e) 3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) with the addition that the reaction mixture was heated to reflux for 20 minutes. Product was purified using reverse phase preparative HPLC (eluent $MeCN/NH_3(aq)$).
1H NMR (DMSO) δ 7.51 - 7.41 (3H, m), 7.24 - 7.12 (4H, m), 7.06 (2H, t), 6.82 (2H, d,), 6.75 (1H, d), 4.68 (2H. s), 2.73 (3H, s)
MS: APCI- [M-H] 438

Example 26
3-[(4-chlorophenyl)sulfonyl]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid, ammonium salt



a) 5-fluoro-2-methyl-1*H*-indole-1-acetic acid methyl ester

A mixture of 5-fluoro-2-methylindole (2.4 g) , cesium carbonate (16.6 g) and methyl bromoacetate (5.4 ml) in acetone 240 ml was stirred and heated under reflux for 16 h. The solvent was removed, water and ethyl acetate were added and the organic phase separated. The aqueous phase was re-extraced with ethyl acetate and the combined organic solution dried and concentrated to a solid. Purification by flash chromaography using dichloromethane:ethylacetate gave the subtitle compound as a solid (2.9g)

MS: APCI+ [M+H] 222

b) 5-fluoro-2-methyl-1*H*-indole-1-acetic acid

The product from step a) was dissolved in THF (30ml) and a solution of LiOH.H20 (0.91g) in H_20 (10ml) was added. After 24h the solvent was removed, 10% (aq) HCl and ethyl acetate were added and the organic phase separated. The aqueous phase was re-extraced with ethyl acetate and the combined organic solution washed with brine, dried and concentrated to an oil. Purification by flash chromaography using dichloromethane:ethylacetate gave the subtitle compound as a yellow powder (1.2 g).

MS: APCI $[M-H]^-$ 206

c) 3-[(4-chlorophenyl)thio]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

Iodine (0.98 g) was added to a solution of 4-chlorolbenzenethiol (0.55 g) and the product from step b) (0.4 g) in NMP (5 ml). The solution was stirred for 24 h and the crude product purified by reverse phase chromatography to give the subtitle compound as a solid (0.29 g)

MS: APCI $[M-H]^-$ 348/50

^{1}H NMR (DMSO) δ 7.4 (1H, m), 7.25(2H, d), 7.0-6.9 (4H, m), 4.59 (2H, s), 2.37 (3H, s).

d) 3-[(4-chlorophenyl)sulfonyl]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid, ammonium salt

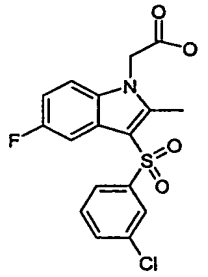
3-Chlorobenzenecarboperoxoic acid (0.4 g) was added to a solution of the product from step c) (0.19 g) in acetonitrile (4 ml). The reaction was stirred for 3 h, 1M aqueous sodium thiosulphate (5 ml) was added and stirred for a further 15 min, 10%aqu HCl and ethyl acetate were added and the organic phase separated. The aqueous phase was re-extracted with ethyl acetate and the combined organic solution washed with brine, dried and concentrated to a solid which was purified by reverse phase chromatography to give the title compound as a solid (0.12 g)

MS: APCI $[M-H]^-$ 380/82

^{1}H NMR (DMSO) δ 7.94 (2H, m), 7.62(2H, m), 7.6-7.55 (2H, m), 7.4-6.8 (1H bs), 7.05 (1H, dt), 4.8 (2H, s), 2.61 (3H, s).

Example 27

3-[(3-chlorophenyl)sulfonyl]-5-fluoro-2-methyl- 1*H*-indole-1-acetic acid, ammonium salt



a) 3-[(3-chlorophenyl)thio]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid

Prepared by the method of example 26 step c) using the the product of example 26 step b) (0.55g), iodine (0.98g) and 3-chlorolbenzenethiol to give the subtitle compound as a solid (0.25 g)

MS: APCI $[M-H]^-$ 348/50

^{1}H NMR (DMSO) δ 7.4 (1H, m), 7.2(1H, m), 7.16 (1H, m), 7.0-6.95 (4H, m), 4.57 (2H, s), 2.28 (3H, s)

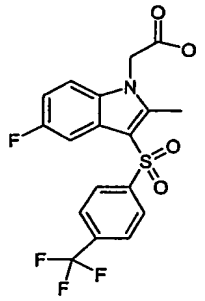
b) 3-[(3-chlorophenyl)sulfonyl]-5-fluoro-2-methyl- 1*H*-indole-1-acetic acid, ammonium salt

Prepared by the of example 26 step d) using the the product of example 27 step a) (0.15g) and 3-chlorobenzenecarboperoxoic acid (0.32 g) to give the title compound as a solid (0.09 g).

MS: APCI $[M-H]^-$ 380/82

^{1}H NMR (DMSO) δ 7.94 (2H, m), 7.7(1H, m), 7.6 (2H, m), 7.55 (1H, m), 7.2-7.0 (1H bs), 7.05 (1H, dt), 4.79 (2H, s), 2.63 (3H, s).

Example 28
5-fluoro-2-methyl-3-[[4-(trifluoromethyl)phenyl]sulfonyl]- 1*H*-indole-1-acetic acid, ammonium salt



a) 5-fluoro-2-methyl-3-[[4-(trifluoromethyl)phenyl]thio]-1*H*-indole-1-acetic acid

Prepared by the method of example 26 step c) using the the product of example 26 step b) (0.55g), iodine (0.98g) and 4-trifluoromethylbenzenethiol (0.67g) to give the subtitle compound as a solid (0.25 g).

MS: APCI $[M-H]^-$ 382

^{1}H NMR (DMSO) δ 7.57 (3H, m), 7.05 (2H, m), 7.02 (2H, m), 5.0 (2H, s), 2.4 (3H, s)

b) 5-fluoro-2-methyl-3-[[4-(trifluoromethyl)phenyl]sulfonyl]- 1*H*-indole-1-acetic acid, ammonium salt

Prepared by the method of example 26 step d) using the the product of example 28 step a) (0.17g) and 3-chlorobenzenecarboperoxoic acid (0.33 g) to give the title compound as a solid (0.11 g).

MS: APCI $[M-H]^-$ 414

^{1}H NMR (DMSO) δ 8.18 (2H, d), 7.95 (2H, d), 7.65-58 (2H, m), 7.2-6.9 (1H, bs), 7.14-7.09 (1H, m), 5.02 (2H, s), 2.67 (3H, s).

Pharmacological Data

Ligand Binding Assay

[^{3}H]PGD_2 was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEKcells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100μg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25μg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay

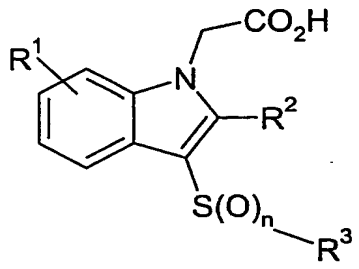
buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

Each assay contained 20µl of 6.25nM [^{3}H]PGD_2, 20µl membrane saturated SPA beads both in assay buffer and 10µl of compound solution or 13,14-dihydro-15-keto prostaglandin D_2 (DK-PGD_2, for determination of non-specific binding, Cayman chemical company). Compounds and DK-PGD_2 were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at room temperature for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC_{50} value of less than (<) 10µM. Specifically example 2 has a $pIC_{50} = 8.1$ example 6 has a $pIC_{50} = 7$ and example 7 has a $pIC_{50} = 6.6$

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which:

n represents 1 or 2;

R^1 is one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter five groups being optionally substituted by one or more substituents independently selected from halogen, OR^7 and NR^8R^9, NR^8R^9, $S(O)_xR^7$ where x is 0, 1 or 2;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter group being optionally substituted by one or more substituents independently selected from halogen atoms, OR^8 and NR^5R^6, $S(O)_xR^7$ where x is 0,1 or 2;

R^3 is aryl or a 5-7 membered aromatic ring containing one or more heteroatoms selected from N, S and O, each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OH, OR^4, SR^4, SOR^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^9SO_2R^4$, $NR^9CO_2R^4$, NR^9COR^4, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, OR^7 and NR^8R^9, $S(O)_xR^7$ where x is 0,1 or 2;

R^4 represents aryl, heteroaryl, or C_1-C_6 alkyl, all of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, heteroaryl, OR^{10}

and $NR^{11}R^{12}$ $S(O)_xR^{13}$ (where x = 0, 1 or 2), $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;

R^5 and R^6 independently represent a hydrogen atom, a C_1-C_6 alkyl group, an aryl,or a heteroaryl, the latter three of which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, OR^{13} and $NR^{14}R^{15}$, $CONR^{14}R^{15}$, $NR^{14}COR^{15}$,$SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$, CN, nitro;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_x$ where x is 0, 1 or 2, NR^{16}, and the ring itself optionally substituted by C_1-C_3 alkyl;

R^7 and R^{13} independently represent a C_1-C_6 alkyl group, an aryl or heteroaryl group all of which may be optionally substituted by halogen atoms;

R^8 represents a hydrogen atom, $C(O)R^9$, C_1-C_6 alkyl (optionally substituted by halogen atoms, aryl or heteraryl groups, both of which may also be optionally substituted by one or more fluorine atoms); an aryl or a heteroaryl group, which may be optionally substituted by one or more halogen atoms;

each of R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6 alkyl, an aryl or a heteroaryl group (all of which may be optionally substituted by one or more halogen atoms); and

R^{16} is hydrogen, C_{1-4} alkyl, $-C(O)C_1$-C_4 alkyl, $C(O)YC_1$-C_4alkyl, Y is O or NR^7.

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which n is 2.

3. A compound according to claim 1 or 2 in which R^1 is halogen, nitrile, C_{1-6}alkyl or SO_2R^4, NO_2, NR^9COR^4, $NR^9SO_2R^4$, aryl, NR^5R^6.

4. A compound according to any one of claims 1 to 3 in which the substituent(s) is/are in the 4- and/or 5- position

5. A compound according to any one of claims 1 to 4 in which R^2 is C_{1-6}alkyl.

6. A compound according to claim 4 in which R^3 is phenyl substituted by halogen..

7. A compound according to claim 1 selected from:

3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid;

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,

4-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(3-methoxyphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(2-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(3-Chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(4-Cyanophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;

3-[(2-methylphenyl)sulfonyl]-2,5-Dimethyl-1*H*-indol-1-acetic acid;

3-[(2-ethylphenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-nitro-1*H*-indole-1-acetic acid;

4-(Acetylamino)-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-[(methylsulfonyl)amino]- 1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-4-(ethylamino)-2-methyl-1*H*-indole-1-acetic acid;

3-[(2,6-Dichlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole-1-acetic acid;

3-[(4-chlorophenyl)sulfonyl]-2-methyl-4-phenyl-1*H*-indole-1-acetic acid

3-[(4-chlorophenyl)sulfonyl]-5-fluoro-2-methyl-1*H*-indole-1-acetic acid,

3-[(3-chlorophenyl)sulfonyl]-5-fluoro-2-methyl- 1*H*-indole-1-acetic acid,

5-fluoro-2-methyl-3-[[4-(trifluoromethyl)phenyl]sulfonyl]- 1*H*-indole-1-acetic acid,

and pharmaceutically acceptable salts thereof.

8. A compound of formula (I) according to any one of claims 1 to 7 for use in therapy.

9. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 7.

10. A method according to claim 9 where the disease is asthma or rhinitis..

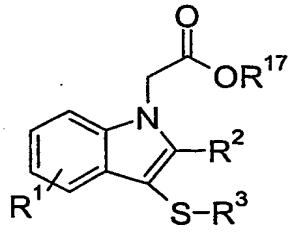
11. Use of a compound of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 7, in the manufacture of a medicament for treating a disease mediated by prostaglandin D2.

12. Use of a compound of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 7, in the treatment of a disease mediated by prostaglandin D2.

13. Use according to claim 11 or 12 where the disease is asthma or rhinitis.

14. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):

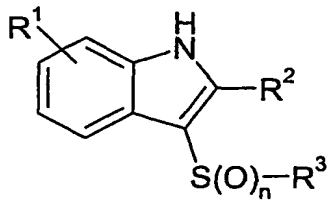
(a) oxidation of a compound of formula (II):



(II)

in which R^{17} is hydrogen or alkyl and R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, or

(c) reaction of a compound of formula (III):



(III)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (IV):

$$R^{18}\text{-}O(CO)CH_2\text{-}L \quad (IV)$$

where R^{18} is an alkyl group and L is a leaving group in the presence of a base, and optionally thereafter (a) or (b) in any order:

- hydrolysing the ester group R^{17} or R^{18} to the corresponding acid
- removing any protecting group
- forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01216

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 209/30, A61K 31/405, A61P 11/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1170594 A2 (PFIZER PRODUCTS INC.), 9 January 2002 (09.01.02), claim 18, page 4, line 52, page 34, compound C --	1-14
A	US 5486525 A (SUMMERS, JR. ET AL.), 23 January 1996 (23.01.96) --	1-14
A	US 5567711 A (SHEPPARD ET AL), 22 October 1996 (22.10.96) -- --------	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2003	17 -11- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer SOLVEIG GUSTAVSSON/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01216

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 9-10 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01216

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1170594 A2	09/01/02	IL 144101 D	00/00/00
		JP 2002098702 A	05/04/02
		US 2002022218 A	21/02/02
US 5486525 A	23/01/96	AT 212992 T	15/02/02
		AU 690620 B	30/04/98
		AU 1303695 A	03/07/95
		BR 1100809 A	23/11/99
		DE 69429827 D,T	21/11/02
		DK 734386 T	27/05/02
		EP 0734386 A,B	02/10/96
		SE 0734386 T3	
		ES 2173171 T	16/10/02
		IL 111963 D	00/00/00
		JP 9507474 T	29/07/97
		PT 734386 T	31/07/02
		WO 9516687 A	22/06/95
US 5567711 A	22/10/96	AT 206425 T	15/10/01
		AU 705237 B	20/05/99
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		CA 2218020 A	24/10/96
		DE 69615676 D,T	11/07/02
		DK 821685 T	21/01/02
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		SE 0821685 T3	
		ES 2164240 T	16/02/02
		IL 117723 A	26/07/00
		JP 11503758 T	30/03/99
		PT 821685 T	28/03/02
		US 5643922 A	01/07/97
		US 5654305 A	05/08/97
		WO 9633196 A	24/10/96